REMARKS

Claims 1-30, 36-39, 58-61, 69-72, and 92-95 have been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of any canceled claims in related applications. Claims 31, 41, 46, 50, 53, 64, 74, 79, 83, and 87 have been amended as discussed in the interview of August 5, 2003. The amendments are fully supported by the specification and original claims and do not introduce any new matter.

Claims 31-35, 40-57, 62-68, 73-91, and 96-107 will be pending upon entry of these amendments. Claims 98-107 were previously allowed.

I. Amendments

A. Amendments to the Sequence Listing

The Second Substitute Sequence Listing filed herewith corrects errors contained in SEQ ID NOS: 1 and 2. Compared with the previous Substitute Sequence Listing (filed July 2, 2001), the following changes have been made to SEQ ID NOS: 1 and 2 in the Second Substitute Sequence Listing filed herewith: (1) in SEQ ID NO:1 nucleotide G-1103 has been changed to C-1103; (2) in SEQ ID NO:1 nucleotide A-1118 has been changed to G-1118; and (3) in SEQ ID NO:2 amino acid E-255 has been changed to D-255. These amendments are consistent with and supported by the Declaration of Craig Rosen which was submitted with the Preliminary Amendment and Substitute Sequence Listing filed on July 2, 2001. The Rosen Declaration stated that the correct sequences of SEQ ID NOS: 1 & 2 are those published in Genbank Accession No. U39613. The assertions made in the Rosen Declaration are, as before, correct. The presently submitted amendments to the sequence listing merely correct inadvertent clerical errors in the previously filed Substitute Sequence Listing and bring the sequence listing into conformance with the correct sequences for SEQ ID NOS: 1 and 2 as described in said declaration. Moreover, the Second Substitute Sequence Listing filed herewith adds SEQ ID NOS:13 and 14, which correspond to two sequences disclosed in Fig. 3 that previously lacked sequence identifiers. Thus, these amendments do not add new matter.

B. Amendments to the Specification

On page 4 of the specification, the third paragraph referring to Figures 1A-B has been amended to include reference to SEQ ID NOS: 1 and 2, corresponding to ICE-LAP 3 polynucleotide and polypeptide, respectively. Likewise, the fourth paragraph on page 4, which refers to Figure 2A-B has also been amended to include reference to SEQ ID NOS: 3 and 4, corresponding to ICE-LAP 4 polynucleotide and polypeptide, respectively. In addition, the fifth paragraph on page 4 that refers to Figures 3A-C, an alignment of ICE-LAP 3, ICE-LAP 4, Human ICE, and ced-3, has been amended to reference SEQ ID NO:14 with Human ICE and SEQ ID NO:13 with ced-3.

II. Formal Matters

A. The Abstract

The abstract of the present application was objected to based on an allegation that it "does not reflect on the subject being claimed, which is the antibodies to the ICE-LAP3 and ICE-LAP4." *See* Paper No. 10 at page 2, paragraph numbered 4. The abstract was also objected to for this same reason in Paper No. 8, at page 3, paragraph numbered 6. In response to Paper No. 8, Applicants traversed the objection to the abstract as follows:

> According to M.P.E.P. 608.01(b), "[a] patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains." M.P.E.P. 600-63, right column, second paragraph, emphasis added. The Guidelines For The Presentation of Patent Abstracts in M.P.E.P. 608.01(b) do not reveal any requirement that the patent abstract should reflect the *claims* pursued in a given application. To the contrary, the patent abstract is intended to reflect the patent *disclosure*. Applicants believe that the existing abstract is a fair reflection of Applicants' disclosure and thus no amendment is required. Withdrawal of this objection is respectfully requested.

See Paper No. 9, at page 6, second full paragraph (emphasis in the original). Applicants maintain the argument presented above, and respectfully request that this explanation be acknowledged and that this objection be reconsidered and withdrawn.

B. The Title

The title of the present application was also objected to as not descriptive. *See* Paper No. 10 at page 2, paragraph numbered 4. The title was objected to for this same reason in Paper No. 8, at page 3, paragraph numbered 6. In response to Paper No. 8, Applicants amended the title in Paper No. 9 at page 1. Applicants maintain that the title as already amended reflects the claims under examination. Therefore, reconsideration and withdrawal of this objection is respectfully requested.

III. Rejections of claims 31, 34-35, 38-39, 42-50, 53, 55-57, 59-83, and 87-97 Under 35 U.S.C. § 112, First Paragraph

A. Claims 31, 53, 64, and 87

Claims 31, 53, 64, and 87, and their dependent claims have been rejected under 35 U.S.C. § 112, first paragraph, because the claimed invention allegedly lacks written description. *See* Paper No. 10, at page 12-16, paragraph numbered 8. In particular, the Examiner rejects sections (c), (d), (g), and (h) of claims 31, 53, 64, and 87 because,

> The specification does not reasonably provide a **written description** of (1) *any* isolated antibody or fragment thereof that specifically binds to a*ny* protein consisting of any portion of SEQ ID NO: 2, wherein said portion "**comprises**" at least 30 or 50 contiguous amino acid residues of SEQ ID NO: 2 or 4...

See Paper No. 10, at page 12, first full paragraph (emphasis in the original).

Applicants respectfully disagree with the preceding argument. However, sections (c), (d), (g), and (h) of claims 31, 53, 64, and 87 have been deleted. Thus, Applicants submit that rejection of claims 31, 53, 64, and 87 (and thereby dependent claims 34-35, 38-39, 42-50, 55-57, 59-63, 65-83, and 88-97) under 35 U.S.C. §112, first paragraph, has been obviated.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112 second paragraph of claims 31, 34-35, 38-39, 42-50, 53, 55-57, 59-83, and 87-97 be reconsidered and withdrawn.

B. Claims reciting antibodies that bind proteins comprising the amino acid sequence of SEQ ID NO: 2 or 4

Claims 31 (c), (d), (g), and (h); 64 (c), (d), (g), and (h); 53; and 87, as well as the claims that depend upon these claims, have been rejected under 35 U.S.C. § 112, first paragraph, over the use of the term "comprising." *See* Paper No. 10, pages 12-16, paragraph numbered 8. In particular, it was asserted that these claims:

> ...recite a protein consisting a portion of...wherein the portion "comprises" at least 30 or 50 contiguous amino acid residues....The term "comprising" is open-ended. It expands the portion to include additional amino acids at either or both end of said portion. There is insufficient written about the undisclosed amino acids to which the claimed antibody binds.

See Paper No. 10, at page 15, last paragraph.

Applicants respectfully disagree; however, sections (c), (d), (g) and (h) of claims 31, 64, 53 and 87 have been deleted, thereby obviating the rejection with respect to claims 31 and 64.

With regard to the rejection of claims 53 and 87, Applicants respectfully disagree and traverse.

Applicants respectfully submit that sections (a), (b), (e), and (f) of claims 53 and 87 (corresponding to sections (a), (b), (c), and (d) as currently amended), encompass antibodies that specifically bind the full length polypeptide, or the full length polypeptide minus methionine, of SEQ ID NO:2 and SEQ ID NO:4; or the polypeptide encoded by the deposited cDNAs, including polypeptide derivatives or analogs in which said polypeptide is fused to a heterologous amino acid sequence. Antibodies that specifically bind ICE-LAP 3 or 4 polypeptide derivatives are supported in specification on page 23, last full paragraph (emphasis added):

> The polypeptides, their fragments or other derivatives, or analogs thereof, or cells expressing them can be used as an immunogen to produce antibodies thereto.

Support for the production of a polypeptide derivative or analog comprising the polypeptide of SEQ ID NO:2, or the polypeptide encoded by ATCC Deposit No. 75875,

and a heterologous amino acid sequence can be found, for example, at pages 29-30, bridging paragraph, where expression of recombinant ICE-LAP 3 is discussed (emphasis added):

> The expression of a plasmid, ICE-LAP-3 HA, is derived from a vector pcDNAI/Amp (Invitrogen) containing: 1) SV40 origin of replication, 2) ampicillin resistance gene, 3) E.coli replication origin, 4) CMV promoter followed by a polylinker region, a SV40 intron and polyadenylation site. A DNA fragment encoding the entire ICE-LAP-3 precursor and a HA tag fused in frame to its 3' end was cloned into the polylinker region of the vector, therefore, the recombinant protein expression is directed under the CMV promoter.

Similar support for the production of a polypeptide derivative or analog comprising the polypeptide of SEQ ID NO:4, or the polypeptide encoded by ATCC Deposit No. 75873, and a heterologous amino acid sequence can be found, for example, at pages 32, first paragraph:

> The expression of a plasmid, ICE-LAP-4 HA, is derived from a vector pcDNAI/Amp (Invitrogen) containing: 1) SV40 origin of replication, 2) ampicillin resistance gene, 3) E.coli replication origin, 4) CMV promoter followed by a polylinker region, a SV40 intron and polyadenylation site. A DNA fragment encoding the entire ICE-LAP-4 precursor and a HA tag fused in frame to its 3' end was cloned into the polylinker region of the vector, therefore, the recombinant protein expression is directed under the CMV promoter.

Thus, in light of the support in the specification for antibodies specific for SEQ ID NO:2 or 4, or the polypeptide encoded by the deposited cDNAs fused to a heterologous amino acid sequence, Applicants respectfully request that the rejection of claims 53 and 87 and their dependent claims be withdrawn.

C. Claims involving production of an antibody fragment in an isolated cell or hybridoma.

Claims 49-50 and 82-83 directed to an isolated cell line or a hybridoma that produces antibody or antibody fragments specific for the polypeptides of the present invention were rejected under 35 U.S.C. § 112, first paragraph for not being enabled by the specification. In particular, it was asserted at page 9, second full paragraph of the

Office Action that,

> With regard to any isolated cell or hybridoma (claims 49-50, and 82-83) that produce "antibody fragment thereof", it is well known that the cell line and hybridoma produce the whole antibody and not the antibody fragment.

With regard to the rejection of claims 50 and 83, Applicants respectfully disagree. However, claims 50 and 83 have been amended to recite "[a] hybdridoma that produces the antibody of claim 31," thereby obviating the rejection with respect to claims 50 and 83.

With regard to the rejection of claims 49 and 82, which recite "[a]n isolated cell line that produces the antibody or fragment thereof of claim 31 or 64," Applicants respectfully disagree and traverse.

As discussed in the interview of August 5, 2003, as well as in paper No. 9, at page 9, first full paragraph, one of skill in the art would know, based on the teachings in the specification and the general knowledge in the art, how to engineer a cell to produce a fragment of the antibody of claim 31 or of claim 64. Whether a cell produces the whole antibody or a fragment of the antibody is merely a question of which coding sequences the cell is engineered with. Thus, claims 49 and 82 are enabled as to their entire scope, and Applicants respectfully request that the rejection of these claims be withdrawn.

In conclusion, for the reasons discussed above and in response to the amendments made herein, Applicants submit that the rejection of claims 31, 34-35, 38-39, 42-50, 53, 55-57, 59-83, and 87-97 under 35 U.S.C. § 112, first paragraph, has been accommodated, obviated, or overcome. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

IV. Rejection Under 35 U.S.C. § 112, Second Paragraph

A. The scope of dependent claims 46 and 79

Claims 46 and 79, which recite labeled antibodies and are dependent on claims 31 and 64, respectively, were rejected as indefinite because each of claims 46 and 79 allegedly is not "narrower in scope than the claim from which it depends." *See* Paper No. 10, at page 16, paragraph numbered 10.

Applicants respectfully disagree and continue to assert that claims 46 and 79 further limit their respective base claims and are proper as argued by Applicants in Paper No. 9, at page 11, third full paragraph. However, Applicants have amended claims 46 and 79 as suggested by the Examiner in Paper No. 10, at page 16, last sentence.

B. Indefiniteness of Claims 53, 64, and 87

In the present Office Action, on page 28, paragraph numbered 24, it was stated:

> Claims 53, 64, and 87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularily point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite....

While Applicants respectfully disagree with this rejection, sections (c), (d), (g) and (h) of claims 53, 64, and 87 have been deleted as noted in part IIA of this response, thereby obviating the rejection.

V. Rejections Under 35 U.S.C. § 102(e)

A. Anticipation of claims 31, 34-35, 38-39, 43-44, and 48-50

Claim 31, and several dependent claims, 34-35; 38-39; 43-44; and 48-50 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly being anticipated by US Patent 5,552,536. *See* Paper No. 10, at page 17-18, paragraph numbered 13. Applicants respectfully disagree with this rejection and traverse.

The '536 patent discloses an ICE-related cysteine protease III (ICE REL-III) which bears the QACRG consensus pentapeptide sequence shared by ICE-related cysteine proteases. This consensus sequence was identified in the instant specification at page 2 and again at page 5, where its presence in ICE-LAP-3 at amino acid residues 259-263 and in ICE-LAP-4 at residues 161-165 is acknowledged. The '536 patent teaches generally making antibodies to ICE REL-III or fragments thereof, but does not teach any particular antigenic epitopes or any actual antibodies.

Regarding alleged anticipation of claim 31 by the '536 patent, the Examiner states:

> The term 'comprising' is open ended. It expands the claimed polypeptide fragment to include additional amino acid residues at either or both ends to read on the reference polypeptide. Thus, the reference teachings anticipate the claimed invention.

See Paper No. 10 at page 17, lines 23-25. With regard to use of the term "comprising," Applicants note that the claim amendments of the present response remove the term "comprising" from claim 31.

In addition, on page 18, paragraph numbered 13 of the Office Action, the Examiner says the following:

> ...the claimed antibody binds to a protein that has a stretch of amino acid sequence such as Gln-Ala-Cys-Arg-Gly surrounding the catalytic cysteine of ICE identical to the reference protein. In the absence of a side-by-side comparison, the claimed antibody also binds to the reference protein and the reference antibody also binds to the claimed protein.

Applicants respectfully disagree.

First, Applicants point out that claim 31 is directed to antibodies that **specifically** bind the polypeptide of SEQ ID NO:2 or 4. Antibodies specific for the polypeptide disclosed in SEQ ID NO:2 or 4 would not be expected to also bind other homologs containing the sequence Gln-Ala-Cys-Arg-Gly. Rather, if an antibody that bound the polypeptide of SEQ ID NO:2 or 4 also were to bind a homologous protein by virtue of the Gln-Ala-Cys-Arg-Gly epitope, then this antibody would be said to "cross-react" with polypeptides homologous to SEQ ID NO:2 or 4, and it would not "specifically" bind to the polypeptide of SEQ ID NO:2 or 4.

Furthermore, Applicants respectfully submit that the distinction between specific binding and cross-reactivity would be readily recognized by those of ordinary skill in the antibody arts as exemplified by the following definition from a 1991 textbook, Immunology: a Synthesis, second edition, Golub and Green, page 23, lines 16-17, and page 27, lines 2-5, attached hereto as Exhibit A (emphasis added):

> *Specificity* is defined as the ability of antibodies produced in response to an antigen to react with that antigen and not with others....Antibody molecules can exhibit great *specificity*, but there are cross-reactions – cases in which antibody to antigen A also reacts with antigen B. This can be due to the presence of the same molecular configuration, or antigenic determinant, on the two antigens....

In agreement with this definition, one embodiment of the present invention describes the use of an antibody specific for the polypeptide of SEQ ID NO:2 or 4, or the polypeptide encoded by ATCC Deposit No. 75875 or 75873, as a means to quantitate the amount of said polypeptide in a heterogeneous mixture of polypeptides. *See* page 17, last paragraph bridging page 18.

Thus, Applicants respectfully submit that the presently amended claim 31 and the its dependent claims do not read on the ICE related cysteine proteinase III of the '536 patent, or upon any of the other cysteine proteinases with homology to SEQ ID NO:2 or 4 that are disclosed in the specification of the present application, i.e., human ICE and ced-3. *See* page 5, first two paragraphs and Figure 3.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) of claims 31, 34-35, 38-39, 43-44 and 48-50 be reconsidered and withdrawn.

VI. Rejections Under 35 U.S.C. § 103(a)

A. Obviousness of claims 31, 34-35, 38-39, 43-44, and 48 over Cerretti *et al.* in view of Campbell *et al.*

Claims 31, 34-35, 38-39, 43-44, and 48 stand rejected as allegedly obvious over Cerretti *et al.* in view of Campbell *et al.* The Applicants respectfully disagree and traverse.

Applicants submit that sections (c), (d), (g) and (h) of claim 31 have been deleted by the present amendments, as noted in part IIA of this response. Thus, rejection of

claim 31 and claims 34-35, 38-39, 43-44, and 48 over recitation of the term "comprising" is obviated.

Furthermore, while Cerretti *et al.* teach interleukin-1ß converting enzyme (ICE), which has a QACRG pentapeptide sequence shared by ICE-LAP-3 at residues 259-263 and ICE-LAP-4 at residues 161-165, Applicants note that Cerretti *et al.* does not teach antibodies to fragments of ICE such as QACRG. Campbell *et al.* teach that "it is customary now for any group working on a macromolecule to both clone the gene encoding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)". Paper No. 10 at page 20, lines 4-6. The Examiner states that Campbell *et al.* teach generally the making of polyclonal and monoclonal antibodies and their use in an ELISA.

The present claims are directed to antibodies that specifically bind amino acid sequences derived from SEQ ID NO:2 or 4. While the QACRG sequence is common to ICE, ICE-LAP-3, and ICE-LAP-4, any antibody that specifically binds only the QACRG pentapeptide sequence (if such exists) would not *specifically* bind the ICE-LAP-3 or ICE-LAP-4 sequences of the present claims. On the other hand, any antibody that does not specifically bind to QACRG alone, but specifically binds an epitope of ICE-LAP-3 or ICE-LAP-4 which includes QACRG, is not an antibody taught or suggested by Cerretti *et al.* Thus, Cerretti *et al.*, either alone or combined with Campbell *et al.*, does not teach or suggest all the characteristics of the antibodies of claim 31 or claims 34-35, 38-39, 43-44, and 48 which depend therefrom.

Withdrawal of the rejection is respectfully requested.

B. Obviousness of claims 31 and 45 over Cerretti *et al.* or U.S. Patent 5,552,536; each in view of Campbell *et al.*

Claims 31 and 45 stand rejected as allegedly obvious over Cerretti *et al.* or U.S. Patent 5,552,536 each in view of Campbell *et al.* The rejection is respectfully traversed.

The teachings of Cerretti *et al.*, U.S. Patent 5,552,536, and Campbell *et al.* have been discussed above.

The combination of either Cerretti *et al.* or the '536 patent with Campbell fails to teach or suggest the antibodies of the instant claims for the same reasons discussed for the preceding rejection (for Cerretti) or for the 102(e) rejection (for the '536 patent).

Neither combination of references teaches or suggests the recited amino acid sequences to which the antibodies specifically bind.

Withdrawal of the rejection is respectfully requested.

C. Obviousness of claims 31, 43-44, and 49-50 over Cerretti *et al.* in view of Harlow *et al.*

Claims 31, 43-44, and 49-50 stand rejected as allegedly obvious over Cerretti *et al.* in view of Harlow *et al.* The rejection is respectfully traversed.

The teachings of Cerretti *et al.* have been discussed above. Harlow *et al.* teach methods of making polyclonal and monoclonal antibodies.

The combination of Cerretti *et al.* and Harlow *et al.* fails to teach or suggest the antibodies of the instant claims for the same reasons discussed above. The combination of references fails to teach or suggest the recited amino acid sequences to which the antibodies specifically bind.

Withdrawal of the rejection is respectfully requested.

D. Obviousness of claims 31, 45-47 over Cerretti *et al.* in view of Harlow *et al.*

Claims 31 and 45-47 stand rejected as allegedly obvious over Cerretti *et al.* in view of Harlow *et al.* The rejection is respectfully traversed.

The teachings of Cerretti *et al.* have been discussed above. Harlow *et al.* teach Fab fragments and methods of labeling antibodies, including labeling with an enzyme.

The combination of Cerretti *et al.* and Harlow *et al.* fails to teach or suggest the antibodies of the instant claims for the same reasons discussed above. The combination of references fails to teach or suggest the recited amino acid sequences to which the antibodies specifically bind.

Withdrawal of the rejection is respectfully requested.

E. Obviousness of claims 31 and 46-47 over U.S. Patent 5,552,536 in view of Cerretti *et al*

Claims 31 and 46-47 stand rejected as allegedly obvious over U.S. Patent 5,552,536 in view of Cerretti et al. The rejection is respectfully traversed.

The teachings of U.S. Patent 5,552,536 and Cerretti et al. have been discussed

above.

The combination of the '536 patent with Cerretti et al. fails to teach or suggest the antibodies of the instant claims for the same reasons discussed above. This combination of references does not teach or suggest the recited amino acid sequences to which the antibodies specifically bind.

Withdrawal of the rejection is respectfully requested.

F. Obviousness of claims 31 and 45 over Cerretti *et al.* or U.S. Patent 5,552,536; each in view of U.S. Patent 5,260,203.

Claims 31 and 45 stand rejected as allegedly obvious over Cerretti et al. or U.S. Patent 5,552,536 in view of U.S. Patent 5,260,203. The rejection is respectfully traversed.

The teachings of Cerretti et al. and U.S. Patent 5,552,536 have been discussed above. U.S. Patent 5,260,203 teaches making single chain antibodies.

The combination of either Cerretti et al. or the '536 patent with the '203 patent fails to teach or suggest the antibodies of the instant claims for the same reasons discussed above. Neither combination of references teaches or suggests the recited amino acid sequences to which the antibodies specifically bind.

Withdrawal of the rejection is respectfully requested.

Conclusion

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the present application. In view of the foregoing amendments and remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Dated: September 3, 2003

Respectfully submitted,

By_____

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